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Vestronidase alfa (UX-003) for mucopolysaccharidosis type VII (MPS 7; Sly syndrome)

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LAY SUMMARY

Mucopolysaccharidosis type VII (MPS 7) is an extremely rare, inherited condition caused by a deficiency of an enzyme called beta-glucuronidase. Normally the enzyme breaks down mucopolysaccharides, however as it is lacking the breakdown does not take place. The incomplete broken down mucopolysaccharides remain stored in cells in the body causing progressive damage. Death in the womb is not uncommen, but if born some babies can show little sign of the disease. However, as more and more cells become damaged, symptoms start to appear.

There are no approved treatments for MPS 7, and people with the condition often die in early infancy, but some have lived for several decades.

Vestronidase alfa (UX 003) is a novel treatment to replace the missing enzyme in MPS 7 patients. Positive outcomes have been reported following a phase III trial in patients aged five to 35, and another trial is ongoing in patients under the age of five.

TARGET GROUP

- Mucopolysaccharidosis type VII (MPS 7; Sly syndrome)

TECHNOLOGY

DESCRIPTION

Vestronidase alfa (UX 003; rhGUS; recombinant human beta glucuronidase) is an investigational enzyme replacement therapy for patients with MPS 7.[1] MPS 7 is a genetic metabolic disorder caused by a deficiency of the lysosomal enzyme beta-glucuronidase, which is required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAGs).[1] The inability to break down GAGs leads to their accumulation in tissues.[1] Vestronidase alfa aims to replace beta-glucuronidase to help break down GAGs.[1]

In a phase III trial, 4 mg/kg of vestronidase alfa was administered intravenously every fortnight, for a minimum of 24 weeks in total.[2] The primary outcome in trials is the reduction of urinary GAG (uGAG) excretion, which a recent cross-sectional analysis linked to longer survival in patients with MPS 7.[3]

Vestronidase alfa is not approved or in trials for any other condition.

INNOVATION and/or ADVANTAGES

If licensed, this drug could provide a long-awaited treatment option for patients with MPS 7 who currently have no other treatments available to them.

DEVELOPER

Ultragenyx Pharmaceutical Inc

AVAILABILITY, LAUNCH or MARKETING

Vestronidase alfa is a designated orphan drug for MPS 7 in the EU[4] and USA.[5]

In July 2016, Ultragenyx announced plans to meet with the FDA and EMA to discuss plans to submit regulatory filings in the first half of 2017.[6]

PATIENT GROUP

BACKGROUND

MPS 7, also known as Sly syndrome, is an ultra-rare disease, an autosomal recessive lysosomal storage disorder (LSD), characterised by the deficiency of beta-glucuronidase.[7] LSDs are a grouping of rare inherited metabolic disorders, all resulting from defects in lysosomal function – the inability to produce specific enzymes leads to cells not functioning properly.[8]

The presentation and progression of MPS 7 varies widely. Some patients show early, severe, multisystemic manifestations, while others have a milder phenotype with later onset.[7] The antenatal form of the disease usually leads to death in utero.[9] Neonatal and childhood forms of MPS 7 also have a very limited life expectancy. Some patients with MPS 7 present with hydrops fetalis (severe generalized oedema) at birth. These children retain an enormous amount of fluid throughout the body and often only survive a few months, more than half not surviving early infancy.[7] However, milder forms of the condition are associated with a more prolonged survival; rare MPS 7 patients with milder manifestations of the disease have survived into their fifth decade.[9]

Most patients with the condition have cognitive impairment, hepatosplenomegaly and skeletal dysplasia[7]. Heart disease and airway obstruction are major causes of death in people with MPS 7.[10]

CLINICAL NEED and BURDEN OF DISEASE

The grouping of lysosomal diseases, including around 50 diseases, occur in about 1 in every 5,000 to 7,000 births.[8] Of the 11 different MPS disorders, MPS 7 is one of the rarest.[6]

As an ultra-rare disorder, precise epidemiological data for MPS 7 is scarce.[7] The global frequency of this disease is estimated to be 1 in 300,000 to 2,000,000, but many patients may be missed due to death in utero or in early infancy, before being diagnosed.[7] The EMA reports a prevalence of about 50 people in Europe,[4] and the manufacturer cites a prevalence of "200 in the developed world".[1]

Only around 40 patients with neonatal to moderate presentation of MPS 7 have been reported since the disease was first described in 1973.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE highly specialised technology guidance. Elosulfase alfa for treating mucopolysaccharidosis type IVa (HST2a). December 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Lysosomal Storage Disorders Service (Children). E06/S(HSS)/c.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Laboratory Services). E06/S/c.

OTHER GUIDANCE

None identified.

CURRENT TREATMENT OPTIONS

There are no approved therapies or cure for MPS 7. Treatment options concentrate on disease management, and supportive or palliative care.[11] These include surgery, oxygen supplementation, antibiotics, non-steroidal anti-inflammatory drugs, and physical therapy.[7] Hematopoietic Stem Cell Transplant therapy has also been trialled to restore the activity of the deficient enzyme, beta-glucuronidase.[11]

Four types of enzyme replacement therapy have been approved for other MPS disorders.[6]

EFFICACY and SAFETY

Trial	NCT02230566; phase III
Sponsor	Ultragenyx Pharmaceutical Inc
Status	Published
Source of Information	Trial registry,[2] company website,[12] company news release[6]
Location	USA
Design	randomized, placebo-controlled, blind-start, single-crossover, phase III trial
Participants	N=12; between 5 and 35 years of age; confirmed diagnosis of MPS 7
Schedule	4 mg/kg of vestronidase alfa was administered fortnightly, for a minimum of 24 weeks in total
Follow-up	48 weeks
Primary Outcomes	percentage reduction in urinary GAG excretion after 24 weeks
Secondary Outcomes	multi-domain responder index, individualized clinical response measure, pulmonary function, walking, shoulder flexion, fine and gross motor function, visual acuity, fatigue, safety, tolerability
Key Results	Primary endpoint of reducing urinary GAG (dermatan sulphate) excretion after 24 weeks of treatment, demonstrating a reduction from baseline of 64.8% ($p<0.0001$).
Adverse effects (AEs)	All patients experienced treatment emergent AEs, which were generally mild to moderate in severity. Six of the eight patients with infusion associated reactions (IARs) on rhGUS treatment had events involving the IV catheter. Two patients that had a single hypersensitivity-type IAR, including one Grade 3 treatment-related anaphylactoid serious adverse event (SAE) that resulted from an infusion rate error. The second patient had mild fever and diaphoresis. No patients demonstrated recurring hypersensitivity reactions to infusions. There were no deaths and no treatment discontinuations or missed infusions due to AEs.
Expected reporting date	-

Trial	UX003-CL203; NCT02418455; phase II
Sponsor	Ultragenyx Pharmaceutical Inc

Status	ongoing
Source of Information	Trial registry,[13] company website[12]
Location	USA
Design	Non-randomised, uncontrolled
Participants	N=15; up to 5 years of age; confirmed diagnosis of MPS 7
Schedule	4 mg/kg of UX003
Follow-up	48 weeks
Primary Outcomes	Efficacy of UX003 (percent reduction of uGAG excretion); Safety and tolerability
Secondary Outcomes	Changes in growth velocity; volume of the liver and spleen
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date noted as March 2018.

Trial	UX003-CL201; NCT01856218; phase I/II	NCT02432144
Sponsor	Ultragenyx Pharmaceutical Inc	Ultragenyx Pharmaceutical Inc
Status		
Source of Information	Trial registry,[14] company news releases[15] [16]	Trial registry[17]
Location	UK	UK
Design	Non-randomised, uncontrolled	Open-label extension study
Participants	N=3; aged 5 to 30 years; confirmed diagnosis of MPS 7	N=20; ages 5 and over
Schedule	IV administration every other week (QOW) for 36 weeks with up to an additional 36 weeks. Initial 12-week treatment period with 2 mg/kg every other week will be followed by a 24-week forced dose titration period to assess the optimal dose.	All subjects will receive 4 mg/kg UX003 every other week (QOW) unless data from prior studies define a different dose either for that subject or the use of UX003 in general.
Follow-up	72 weeks	144 weeks
Primary Outcomes	Safety and tolerability of UX003 as measured by severity and number of Adverse Events; efficacy as determined by reduction of total urinary glycosaminoglycan (uGAG) excretion	Safety of UX003 determined by the incidence and frequency of adverse events
Secondary Outcomes	Walking capacity; stair climbing capacity; pulmonary function	Efficacy of UX003 determined by the percent reduction and change from baseline of uGAG excretion.

Key Results	12 week results: Results from the primary analysis phase show evidence of clearance of lysosomal storage as indicated by the decline in urinary glycosaminoglycan (GAG) excretion and the reduction in liver size. The change in urinary GAG excretion was observed by two weeks after the first dose of rhGUS and declined by approximately 40-50% from baseline after 12 weeks of treatment. Decreases in liver size were observed in the two patients who had enlarged livers at baseline. The 36-week results showed a greater change in urinary GAG excretion at the higher 4 mg/kg dose of rhGUS, with a mean urinary GAG reduction of approximately 60%. Sustained decreases in liver size were observed in the two patients who had enlarged livers at baseline, and an improvement in pulmonary function was observed in the one patient who was able to perform the evaluations.	-
Adverse effects (AEs)	No serious adverse events or infusion-associated reactions were observed in the study. The most common adverse events were consistent with the symptoms of MPS 7 or related to intravenous administration of the investigational therapy, including respiratory disorders, infections, and arthralgia.	-
Expected reporting date	-	Estimated primary completion date December 2018

ESTIMATED COST and IMPACT

COST

The cost of the treatment is unknown, and there are no comparator treatments for MPS 7.

The enzyme replacement treatment for MPS IVa, for which NICE guidance exists, has a cost per year of £394,680 per patient.[18]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival	☐ Reduced symptoms or disability
☐ Other	☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services	☐ Decreased use of existing services
☐ Re-organisation of existing services	☐ Need for new services
☐ Other	☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs	☐ Reduced drug treatment costs
☒ Other increase in costs: *new treatment option for this population (but a very small cohort)*	☐ Other reduction in costs
☐ Other	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

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